Original Article

Clinical Signatures of COPD Etiotypes and Phenotypes: A Prospective Cohort Study from India

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder with varied clinical and etiological characteristics. Classification by phenotypes and etiologies provides a multidimensional framework for patient management. Indian data on this heterogeneity remain limited, particularly in settings with biomass exposure and post-tuberculosis (post-TB) lung disease. **Material and Methods:** In this prospective observational study, 60 adults hospitalized with acute COPD exacerbations at a tertiary center in Haryana, India, were evaluated. GesEPOC phenotypes and GOLD 2023 etiotypes categorized patients. Clinical characteristics, exposure history, CAT and mMRC scores, BMI, BODE index, spirometry, and arterial blood gas findings were analyzed. **Results:** The mean age was 61.2 ± 9.8 years, and 70% were men. Environmental etiotypes predominated (58.3%), followed by infectious/post-TB (30.0%). Exacerbator–emphysema (40.0%) and exacerbator–chronic bronchitis (43.3%) were the most frequent phenotypes. The mean CAT and mMRC scores were 20.7 ± 5.8 and 2.6 ± 0.9, respectively, with a median BODE index of 5 (IQR: 3–7). Hypoxemia and hypercapnia occurred in 36.7% and 30.0% of the patients, respectively. Post-TB COPD was associated with a greater symptom burden and lower FEV_1 ($p < 0.05$). **Conclusion:** COPD in this North Indian cohort showed distinct etiological and clinical heterogeneity. Environmental and infectious etiotypes with frequent-exacerbator phenotypes underscore the need for exposure-specific etiotype-based management strategies in tuberculosis-endemic, biomass-exposed settings. **Keywords:** COPD; phenotypes; etiotypes; post-tuberculosis lung disease; biomass exposure.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. It is the second most common cause of death in India, contributing to over one million annual deaths.[1,2] While COPD has classically been defined by persistent airflow limitation, it is now recognized as a syndrome with multiple clinical and biological subtypes shaped by heterogeneous exposures and inflammatory responses.[3,4]

Although spirometry remains the diagnostic cornerstone, it does not capture the full complexity of the disease. Individuals with similar airflow limitations often differ in terms of symptom severity, exacerbation frequency, systemic inflammation, and prognosis.[5,6] This recognition has prompted the development of two complementary frameworks.

Phenotypes describe observable clinical patterns (e.g., emphysema-predominant, chronic bronchitis, frequent exacerbator, or asthma–COPD overlap [ACO]).[7] Etiotypes identify causative exposures or biological mechanisms such as tobacco smoke, biomass fuel, tuberculosis-related scarring, asthma-associated inflammation, and rare genetic or developmental causes.[8–11]

This multidimensional model is particularly relevant in India. The population exhibits a distinct exposure mosaic: tobacco smoking dominates in men. In contrast, biomass smoke exposure from wood or dung combustion remains pervasive among women, and post-tuberculosis COPD (PTB-COPD) is increasingly prevalent in regions with endemic TB. Regional hospital-based reports and national surveys also document substantial COPD prevalence and a high burden of biomass-related diseases in India, reinforcing the need for a context-specific study of phenotypes and etiotypes.[12-14]

Biomass COPD is typically airway dominant, with less emphysema but greater small-airway obstruction.[8] In contrast, PTB-COPD often presents with parenchymal fibrosis, bronchiectasis, and volume loss, leading to chronic airflow obstruction and frequent exacerbations.[9,10]

However, systematic studies integrating both frameworks (phenotype and etiotype) in the Indian COPD population are

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scarce. Most prior studies have focused on either spirometry or isolated risk factors. A unified approach may better reflect the interplay between environmental exposure, clinical manifestations, and disease severity.[11]

We hypothesized that COPD etiotypes defined by environmental versus infectious exposures would demonstrate distinct symptom, functional, and systemic profiles, independent of spirometric severity.

Given these considerations, the present study aimed to systematically evaluate the clinical, functional, and radiological characteristics of COPD in an Indian cohort, stratified by etiologies and phenotypes, to inform tailored management strategies.

Materials and Methods

Study design and setting: This prospective, hospital-based observational study was conducted between January 2023 and June 2024 at the Department of Respiratory Medicine, Shaheed Hasan Khan Mewati Government Medical College (SHKM GMC), Nalhar, Nuh, Haryana, a tertiary referral center serving semi-urban and rural populations in northern India. This study aimed to characterize the clinical and functional profiles of patients with chronic obstructive pulmonary disease (COPD) stratified by both phenotype and etiotype, in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 and GesEPOC 2021 frameworks.[12,13] Consecutive eligible admissions with AECOPD were approached for enrollment, and screening logs were maintained to document the enrollment rates and reasons for non-inclusion.

A target sample of 60 patients was chosen based on the center's annual AECOPD admission rates and feasibility for exploratory analysis. This study was intended to be hypothesis-generating and to provide effect-size estimates for future multicenter sample-size calculations.

Participants and eligibility criteria: Consecutive adults aged ≥40 years who were admitted with acute exacerbations of COPD (AECOPD) were screened. COPD diagnosis required post-bronchodilator $FEV_1/FVC < 0.70$, bronchodilator reversibility <12%, and <200 mL on spirometry performed according to ATS/ERS standards (12). For patients with a first-time diagnosis during the index admission, spirometry was repeated ≥6 weeks after clinical recovery to confirm persistent airflow limitation, in line with guideline recommendations. All participants provided written informed consent.

The exclusion criteria were as follows: active or recent pulmonary tuberculosis (within 6 months), interstitial lung disease, pneumothorax, primary lung cancer, prior thoracic radiation, unstable cardiovascular or neurological illness precluding testing, pregnancy, and inability to perform reliable spirometry.

Classification (etiotypes and phenotypes): Participants were assigned etiotypes (GOLD 2023) and phenotypes (Spanish Group of Experts on COPD 2021) as

Etiotypes (GOLD 2023): Environmental (tobacco, biomass, occupational exposure, or ambient air pollution), infectious (post-tuberculosis or other chronic infection–related sequelae such as healed bacterial bronchiectasis), asthma-associated (based on historical features, bronchodilator response, and/or blood eosinophilia), and other (genetic/developmental).

Phenotypes (GesEPOC 2021): Non-exacerbator, Exacerbator–emphysema, Exacerbator–chronic bronchitis, Asthma–COPD overlap (ACO).

Etiotype decision algorithm (operational rules): If documented prior tuberculosis with persistent radiological sequelae (fibrosis/traction bronchiectasis) and clinical features consistent with post-TB damage, classify as Infectious/post-TB regardless of smoking history.

Suppose there is no history of prior TB and predominant exposure to tobacco (>10 pack-years) or long-term biomass exposure with compatible clinical/radiological features. In that case, the case is classified as an environmental case.

In dual-exposure cases (e.g., prior TB + heavy smoking), the dominant etiotype was assigned by consensus of two senior pulmonologists (KS, VG) based on the balance of exposure history, radiology (pattern and distribution), and clinical features; a third reviewer adjudicated disagreements.

Clinical and functional assessment: A structured case record form captured demographics, exposure history (pack-years, biomass type/duration, and kitchen ventilation), comorbidities, exacerbation history, and prior hospitalizations. Symptom burden and health status were assessed using the mMRC and CAT scales.[14,15] Exercise capacity was measured using the 6-minute walk test (6 MWT) according to ATS guidance,[14] and the shorter of the two attempts was selected. Nutritional status (BMI) and BODE index were calculated.[16]

Spirometry was performed using a calibrated spirometer by trained technicians, and included pre- and post-bronchodilator FEV_1, FVC, and FEV_1/FVC. Arterial blood gases (room air) recorded PaO_2, $PaCO_2$, and A-a gradients on admission.

Radiological assessment: All patients underwent chest radiography and thoracic HRCT (128-slice, inspiratory phase) examinations. HRCT scans were visually scored using a semi-quantitative lobar scoring system for emphysema and fibrosis (0–5 per lobe) by two independent radiologists blinded to the clinical data. Inter-rater agreement (Cohen's κ) was calculated for the key characteristics. A concise summary of the structural patterns (fibrosis/bronchiectasis predominance in post-TB; airway wall thickening in biomass-exposed patients) is provided in the Results section, and detailed quantitative imaging analyses are reported in a companion manuscript.

Missing data and data quality: The data completeness was prospectively monitored. Variables with <5% missingness were analyzed using complete-case analysis. For any variable exceeding 5% missingness, multiple imputation (chained equations) would have been used as a sensitivity analysis; in the current cohort, missingness was <5% for primary variables, so complete-case analysis was used as the primary approach. Data entry checks and random audits of 10% of files were performed.

Statistical analysis: Analyses were performed using SPSS v19.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± SD or median (IQR), as appropriate. Categorical variables are presented as numbers (percentages). Group comparisons used independent-samples t-test or ANOVA (with post-hoc Bonferroni correction) for normally distributed continuous variables and Mann–Whitney U or Kruskal–Wallis

for non-normal distributions. Categorical comparisons were made using the χ^2 or Fisher's exact tests.

Correlation analyses (Pearson or Spearman according to distribution) were used to examine the relationships between CAT score, mMRC dyspnea scale score, FEV_1% predicted, BODE index, and A-a gradient.

Multivariable modelling: To address confounding, pre-specified multivariable models were planned for primary outcomes: (a) FEV_1% % predicted (linear regression) and (b) CAT score (linear regression), and for binary outcomes (e.g., hypoxemia) using logistic regression. The a priori selected covariates included age, sex, BMI, smoking exposure (pack-years), and comorbidity. To avoid overfitting, given the modest sample size, we limited the models to no more than one predictor per ten events. Variance inflation factors (VIF) were calculated to assess collinearity, and residual diagnostics were examined for linear models. Where multivariable modelling proved underpowered, adjusted associations were presented as descriptive findings, and a recommendation to validate in a larger multicenter cohort was made. Statistical significance was set at $p < 0.05$. Where relevant, 95% confidence intervals are reported.

Results

Demographic and Exposure Profile: Among the 60 patients, the mean age was 61.2 ± 9.8 years, and 42 (70%) were male. Current smoking was reported by 22 (36.7%) women, former smoking by 24 (40.0%), and 14 (23.3%) were never smokers, predominantly biomass-exposed women. Biomass exposure was present in 14 (23.3%) patients, typically over >10 years of exposure to wood or dung fuel in poorly ventilated settings. Environmental etiotype (tobacco/biomass) accounted for 35 (58.3%) cases, infectious/post-tuberculosis for 18 (30.0%), and asthma-associated for 5 (8.3%), reflecting the dual influence of environmental and contagious exposure in this region [Tables 1 and 2, Figure 1]. After analyzing demographic and exposure characteristics, we examined the distribution of COPD phenotypes in the study cohort.

Table 1: Sociodemographic profile of COPD patients (N = 60)

Variable	Total cohort (N = 60)
Age (years), mean ± SD	61.2 ± 9.8
Sex (Male : Female)	42 (70.0%) : 18 (30.0%)
Smoking status	Current: 22 (36.7%) Former: 24 (40.0%) Never: 14 (23.3%)
Biomass exposure	14 (23.3%), predominantly female
Education level	Majority primary or below
Occupation	Agriculture/manual labor predominant
Comorbidities (any)	42 (70.0%)
– Cardiovascular disease	8 (13.3%)
– Diabetes mellitus	9 (15.0%)
– Hypertension	12 (20.0%)

Table 2. Distribution of COPD phenotypes and etiotypes

Category	n (%)
Phenotypes	
Non-exacerbator	6 (10.0%)
Exacerbator–emphysema	24 (40.0%)
Exacerbator–chronic bronchitis	26 (43.3%)
Asthma–COPD overlap (ACO)	2 (3.3%)
Etiotypes	
Environmental (tobacco/biomass)	35 (58.3%)
Infectious (post-TB/chronic infection)	18 (30.0%)
Asthma-associated	5 (8.3%)
Other/genetic	2 (3.3%)

Table 3: Clinical symptoms and multidimensional indices

Variable	Total (N = 60)
Cough > 2 months	37 (61.7%)
Breathlessness	47 (78.3%)
Wheeze	52 (86.7%)
Chest tightness	31 (51.7%)
CAT score, mean ± SD	20.7 ± 5.8
CAT ≥ 20	34 (56.7%)
mMRC grade, mean ± SD	2.6 ± 0.9
BMI (kg/m²), mean ± SD	21.5 ± 3.6
BODE index, median (IQR)	5 (3–7)

Table 4: Spirometry and arterial blood gas (ABG) parameters

Parameter	Total (N = 60)
Post-BD FEV_1 (% predicted)	46 ± 13
Post-BD FVC (% predicted)	~60
FEV_1/FVC ratio	0.54 ± 0.09

Hypoxaemia (PaO_2 < 60 mmHg)	22 (36.7%)
Hypercapnia ($PaCO_2$ > 45 mmHg)	18 (30.0%)
Elevated A–a gradient	26 (43.3%)
Abbreviations: CAT, COPD Assessment Test; mMRC, Modified Medical Research Council scale; FEV_1 – forced expiratory volume in 1 s; BD, bronchodilator; BMI, body mass index.	

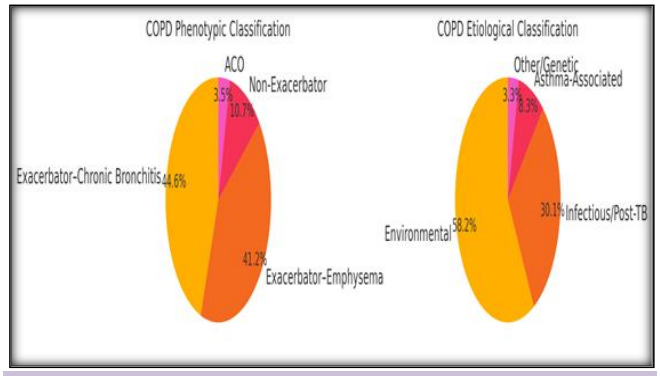

Figure 1: Distribution of COPD Phenotypes and Etiotypes

The figure illustrates the proportional distribution of the COPD subgroups in the study cohort. The left pie chart represents the phenotypic classification, showing that the exacerbator–chronic bronchitis (43.3%) and exacerbator–emphysema (40%) phenotypes predominated, followed by the non-exacerbator group (10%) and the asthma–COPD overlap (ACO)phenotype (3.3%). The right pie chart displays the etiological distribution, with environmental exposure–related COPD (58%) being the most frequent, followed by infectious/post-tuberculosis COPD (30%), asthma-associated COPD (8.3%), and other or genetic etiotypes (3.3%).

Phenotypic Distribution: Exacerbator phenotypes were dominant, with 24 (40.0%) and 26 (43.3%) patients classified as having exacerbator emphysema and exacerbator chronic bronchitis, respectively. Non-exacerbators formed 6 (10.0%), and asthma–COPD overlap (ACO) 2 (3.3%) [Table 2 & Figure 1]. Exacerbators were older (mean 63.5 vs. 56.4 years), had higher symptom burden, and lower BMI and FEV_1 values than non-exacerbators ($p < 0.05$), consistent with advanced systemic and airway disease [Table 3 and 4].

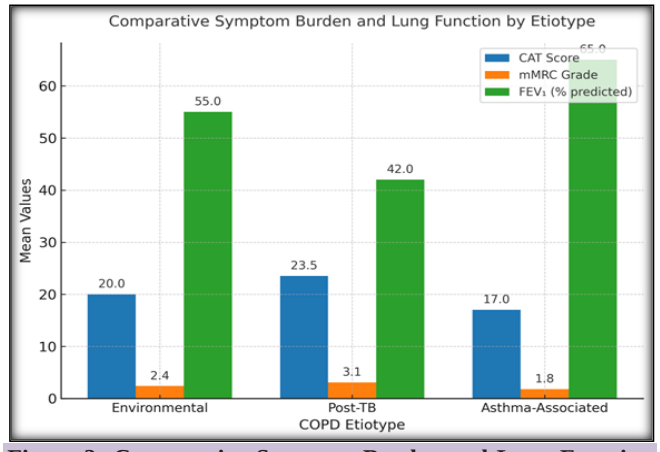

Figure 2: Comparative Symptom Burden and Lung Function by Etiotype

Symptom Burden and Quality of Life: Chronic cough (>2 months) occurred in 37 (61.7%) patients, breathlessness in 47 (78.3%), wheeze in 52 (86.7%), and chest tightness in 31 (51.7%). The mean CAT score was 20.7 ± 5.8, and 34 (56.7%) had CAT scores ≥ 20, indicating severe health status impairment. The mean mMRC grade was 2.6 ± 0.9, with 26 (43.3%) patients reporting a grade ≥ 3 (Table 3). Patients with post-TB COPD had significantly higher CAT (23.1 ± 4.7 vs. 19.6 ± 5.4; p = 0.01) and mMRC (2.9 ± 0.8 vs. 2.4 ± 0.9; p = 0.03) scores than those with environmental COPD, reflecting more debilitating symptoms and restricted exercise tolerance [Figure 2 and Table 3].

This figure presents a comparative analysis of symptom severity and pulmonary function across major COPD etiotypes. The bar chart depicts the mean COPD Assessment Test (CAT) scores, Modified Medical Research Council (mMRC)dyspnea grades, and post-bronchodilator FEV_1 (% predicted) values for the environmental, infectious/post-tuberculosis, and asthma-associated COPD groups. Patients with post-TB COPD demonstrated the highest CAT and mMRC scores and the lowest FEV_1 values, indicating a greater symptom burden and more pronounced functional decline than those with other etiotypes. In contrast, individuals with asthma-associated COPD exhibited relatively preserved lung function and milder symptom indices.

Nutritional Status and Comorbidities: Mean BMI was 21.5 ± 3.6 kg/m², with 25 (41.7%) patients underweight (< 20 kg/m²). Nutritional depletion was particularly marked among exacerbator–emphysema phenotypes (mean BMI 19.8 ± 2.9; p < 0.05) [Table 3]. Comorbidities were common; 42 (70.0%) patients had ≥ 1 systemic illness, including hypertension (20%), diabetes (15%), and cardiovascular disease (13.3%). The coexistent metabolic and cardiovascular burden paralleled that observed in large COPD cohorts (ECLIPSE and COPD Gene) [Table 1].

Functional Impairment: The mean post-bronchodilator FEV_1 was 46 ± 13% predicted, with an FEV_1/FVC ratio of 0.54 ± 0.09, confirming moderate to severe obstruction. The median BODE index was 5 (IQR 3–7) and was significantly higher in patients with exacerbator than in those with non-exacerbator phenotypes ($p < 0.01$) (Table 4). Arterial blood gas analysis revealed hypoxemia (PaO_2 < 60 mmHg) in 22 (36.7%) patients and hypercapnia ($PaCO_2$ > 45 mmHg) in 18 (30.0%) patients. Patients with post-TB COPD exhibited lower FEV_1 (41 ± 10%) and higher A-a gradients (p = 0.02) than those with environmental COPD, indicating more extensive parenchymal and gas exchange impairments [Table 4 & Figure 2].

Discussion

This prospective study provides an integrative clinical and functional characterization of chronic obstructive pulmonary disease (COPD) using dual etiotypes (exposure-based) and phenotypes (clinical pattern-based) in an Indian cohort. By analyzing 60 hospitalized patients, we demonstrated that COPD in India is not a homogeneous, smoking-driven disorder but

rather a mosaic of overlapping disease pathways shaped by environmental, infectious, and inflammatory exposures. These findings reinforce the need for exposure-sensitive, multidimensional approaches to COPD management in low- and middle-income countries (LMICs).

Etiological Diversity and Contextual Relevance: In our study, environmental (tobacco/biomass) and infectious/post-tuberculosis (post-TB) etiotypes together accounted for nearly 90% of cases, underscoring the unique exposure ecology in India. This contrasts with Western cohorts, where smoking-related COPD predominates (>80%).[1,2,17,18] The coexistence of biomass exposure among women and post-tuberculosis damage among men creates a dual burden that is not adequately represented in conventional COPD classification.

Similar findings have been reported in South Asian and Latin American cohorts, where biomass-related COPD manifests with small-airway narrowing, mucus hypersecretion, and less emphysema.[8,19,20] In contrast, post-TB COPD exhibits mixed obstructive–restrictive physiology driven by parenchymal fibrosis and traction bronchiectasis.[9,10] These mechanisms were reflected clinically by higher symptom scores and hypoxemia in the infectious etiotype subgroup.

Comparable exposure–phenotype heterogeneity has also been observed in Indian studies, such as the ICMR-INCARE registry and the AIIMS Delhi COPD cohort, supporting the local applicability of the etiotype concept.[21,22]

Phenotypic Patterns and Clinical Expression: Exacerbator phenotypes predominated, accounting for over 80% of patients, consistent with prior hospital-based cohorts, in which frequent exacerbators represented the most symptomatic subgroup.[11,16] Exacerbator–emphysema patients were leaner and more hypoxaemic, whereas exacerbator–chronic bronchitis types reported higher sputum volume and systemic comorbidities. This mirrors the ECLIPSE and SPIROMICS studies, in which exacerbator phenotypes displayed increased systemic inflammation and poorer health status despite similar spirometric impairments.[18–20]

Symptom–Function Discordance: A key finding was the dissociation between spirometric severity and symptom burden. Despite moderate airflow limitation (mean $FEV_1 \approx$ 45–50% of the predicted value), the CAT scores averaged 20.7, and mMRC grades were ≥2, indicating substantial quality-of-life impairment. Similar observations have been made worldwide.[5,6,23]

This mismatch likely reflects systemic inflammation, nutritional depletion, and comorbidities prevalent in resource-limited settings. Consequently, spirometry alone may underestimate the impact of the disease, particularly in patients with biomass or post-TB etiotypes.

Post-Tuberculosis COPD: Post-TB COPD has emerged as a distinct clinical pattern characterized by a higher symptom burden, lower FEV_1, and greater gas exchange abnormalities. These findings are consistent with those of prior studies showing severe, non-reversible obstruction due to structural lung damage.[9,10,14,24]

While the data suggest that post-TB COPD behaves differently from environmental forms, we have tempered our conclusion to note that this distinction is suggestive rather than definitive, given the modest sample size of this study. Future multicenter studies are required to confirm these patterns.

Nutritional and Systemic Implications: Nearly half of the cohort was underweight (BMI <20 kg/m²), and the mean BODE index was 5, indicating moderate-to-severe systemic involvement. Undernutrition is common in infectious and biomass-related COPD, suggesting a synergistic effect of inflammation, hypoxia, and socioeconomic deprivation on nutritional status.

These findings align with those of previous studies linking low BMI to increased mortality and exacerbation risks.[16,15] Integrating nutritional rehabilitation and exercise conditioning into COPD management is especially important in India's undernourished population.

Statistical adjustments and robustness: We pre-specified multivariable analyses to adjust for potential confounders (age, sex, BMI, pack-years, and comorbidity count), as described in the Methods. Given the exploratory sample size, multivariable models were constrained to avoid overfitting; where models were underpowered, we reported adjusted estimates cautiously and emphasized the need for further validation. Correlation analyses between symptom scores (CAT/mMRC), spirometry, and the BODE index were conducted to evaluate the symptom–function discordance noted in previous cohorts.[5,6] These analytical steps increase confidence that the observed differences are not solely due to confounding, although residual confounding cannot be ruled out.

Radiological correlates: The HRCT patterns in this cohort showed expected trends (post-TB patients with fibrotic changes and bronchiectasis; environmental COPD with airway wall thickening and variable emphysema). Detailed quantitative imaging analyses and inter-rater reliability metrics have been reported in similar HRCT correlation studies (Singh et al., 2020) (28). Here, we report semi-quantitative radiological observations to contextualize these findings.

Public Health and Policy Implications: Our data reinforce that COPD in India represents a spectrum of exposure-driven syndromes rather than a single disease entity. The dual framework of etiotypes and phenotypes offers a pathway for personalized COPD management.

At the public health level, interventions should address the adoption of clean fuels, TB control, and early screening among high-risk populations. Incorporating exposure-specific COPD classification into India's National Programme for Control of Respiratory Diseases (NPCRD) could improve case detection and tailored management. Although the current GOLD framework is universal, it should be contextualized for LMIC populations, where biomass and tuberculosis are more common causal pathways than tobacco.

From a clinical standpoint, recognizing these subgroups enables the development of targeted therapies.

Emphysema-dominant COPD: long-acting bronchodilators, pulmonary rehabilitation, and volume reduction strategies.

Chronic bronchitis phenotypes: mucolytics, macrolides, and anti-inflammatory agents.

Post-TB COPD: Airway clearance, prolonged antibiotics, and management of residual infection or fibrosis.

ACO: inhaled corticosteroid–containing regimens guided by

eosinophil counts.

Strengths and limitations: The strengths of this study include its prospective design, comprehensive phenotypic and etiotypic classification, and use of validated indices (CAT, mMRC, and BODE). This cohort reflects the realistic spectrum of COPD seen in Indian tertiary care settings. The primary limitation of this study is its modest sample size and single-center design, which may limit its generalizability. Selection bias toward hospitalized exacerbators could over-represent patients with severe disease. Furthermore, radiological correlates and long-term outcomes addressed in companion manuscripts will provide deeper mechanistic insights.

Future directions: Larger multicentric studies incorporating radiological, biomarker, and genomic data are needed to refine COPD subtyping and establish etiology-specific management strategies. Prospective follow-up examining exacerbation frequency, hospitalization, and mortality would help to validate the prognostic implications of this dual classification. Additionally, health-economic studies evaluating the cost-effectiveness of personalized COPD interventions in India are needed.

Conclusion

In conclusion, this study demonstrates that COPD in India is a clinically and biologically heterogeneous disorder shaped by unique exposures, such as biomass smoke and tuberculosis. Environmental and infectious etiotypes dominate, and exacerbator phenotypes are the most common. The high symptom burden, nutritional compromise, and physiological impairment observed call for integrated exposure-sensitive strategies. Recognizing and managing COPD through the combined lens of phenotype and etiotype can enable precision respiratory care and improve outcomes in high-burden resource-limited settings.

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Conflicts of interest

There are no conflicts of interest.

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